Reducing Premature Cardiovascular Morbidity and Mortality in People With Atherosclerotic Vascular Disease

The World Heart Federation Roadmap for Secondary Prevention of Cardiovascular Disease

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1. BACKGROUND

1.1. The importance of secondary cardiovascular prevention

Every year, around 35 million people have an acute coronary or cerebrovascular event. About one quarter of these events occur in individuals with known atherosclerotic vascular disease. The number of people with prevalent cardiovascular disease (CVD) worldwide is likely to be around 100 million [1–3]. The five-year rate of recurrent myocardial infarction, stroke, heart failure or cardiovascular death among patients with known CVD is between 20% and 30%, which has been estimated to be four to five times greater than the rate among moderate- and high-risk individuals without known CVD [4]. Such individuals are eligible for secondary preventive therapies (Box 1).

BOX 1. What is secondary prevention?

Secondary cardiovascular prevention can be defined as any strategy aimed at reducing the probability of a recurrent cardiovascular event in patients with known atherosclerotic CVD, including coronary artery disease, cerebrovascular artery disease, peripheral artery disease, and atherosclerotic aortic disease.

Individuals with clinical vascular disease (ischemic heart disease, cerebrovascular disease, or peripheral vascular disease) can be readily identified. Treatment with four proven drugs and smoking cessation will prevent or postpone as many as 75% to 80% of recurrent vascular events and their complications, including death and disability [1] (Box 2)

Secondary prevention can also reduce healthcare costs, increase economic productivity and improve quality of life. These interventions are highly cost-effective (defined as cost per disability-adjusted life year [DALY] saved less than three times GDP per capita) [5].

BOX 2. Secondary prevention interventions

Priority secondary prevention medications:
- **Aspirin**
- **ACE inhibitors**
- **Statins**
- **Beta-blockers***

Lifestyle interventions (cardiac rehabilitation, or preventive cardiology)
- Smoking cessation
- Physical activity
- Healthy diet
- Stress management

*Beta-blockers are recommended for patients with ischemic heart disease. For patients with other types of vascular disease, such as prior ischemic stroke or prevalent peripheral artery disease, recommendations are similar with regard to statin, aspirin, and ≥1 blood pressure-lowering agent (often an ACE inhibitor or angiotensin receptor blocker). ACE = angiotensin converting enzyme.

1.2. Effect of secondary cardiovascular prevention interventions

Secondary prevention of CVD consists of both medication use and behavioral strategies for risk factor management.

Pharmacotherapy

Medications proven to reduce recurrent events and death include antiplatelet agents, renin–angiotensin–aldosterone system antagonists, beta-blockers, and lipid-lowering therapy with statins [6–8].

Behavioral interventions

Additionally, tobacco cessation among individuals who use tobacco, moderate levels of physical activity, healthy diet, weight management and diabetes control are all beneficial for vascular disease prevention.

Smoking is an established risk factor for CVD. Among patients with known CVD, smoking cessation is associated with a substantial reduction in all-cause mortality [9].

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Box 3 summarizes some of the most effective smoking cessation strategies. WHO has developed a training package to assist countries to provide tobacco dependence treatment by integrating brief tobacco interventions (brief advice) into primary care (www.who.int/tobacco/ publications/building_capacity/training_package/treating tobaccodependence/en/).

BOX 3. Individual smoking cessation strategies

- Brief advice from healthcare workers
- Telephone support
- Text messaging
- Printed self-help materials
- Community support
- Multi-session, face-to-face counselling
- Behavioral support
- Pharmacologic support (varenicline, buproprion or nicotine replacement therapy)

Most major cardiology societies and international health organizations have published guidelines recommending evidence-based interventions for secondary CVD prevention [6–8]. These interventions include the use of four proven medications (aspirin, angiotensin-converting enzyme [ACE] inhibitors (or angiotensin receptor blockers if ACE inhibitors are not tolerated), beta-blockers

FIGURE 1. Number of drugs taken by patients with known CVD [11]. A. Coronary heart disease: drugs counted were aspirin, beta-blockers, ACE inhibitors or ARBs, or statins. B. Stroke: drugs counted were aspirin, statins, ACE inhibitors or ARBs, or other blood-pressure-lowering drugs (e.g., beta-blockers, diuretics, and calcium-channel blockers). ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

and statins), as well as lifestyle interventions like smoking cessation, physical activity and healthy diet.

Programs that provide comprehensive management of patients with known CVD are called 'cardiac rehabilitation, or preventive cardiology programs' and consist of a multidisciplinary approach of exercise, education and behavioral modification. They are designed to return the patient to full physical, emotional, psychosocial and vocational function by stabilizing and stopping the underlying atherosclerotic process.

These comprehensive preventive cardiology programs are also important but the challenges of their implementation are complex, particularly in limited resource settings and alternative models for these settings are needed to improve health behaviors.

Further discussion on behavioral interventions for secondary CVD prevention is beyond the scope of this Roadmap but is an area of active interest within the World Heart Federation (WHF).

1.3. The CVD secondary prevention care gap

A care gap refers to a discrepancy between best practice (based high-quality evidence) and the care provided in usual clinical practice. Care gaps include those situations in which proven efficacious interventions are under-utilized. They are seen in practically all countries, including those that are wealthy, but they are most marked in poorer countries, particularly in rural and under-resourced settings. Recently, the Population Urban Rural Epidemiology (PURE) cohort study assessed the use of secondary prevention drugs across high-, middle-, and low-income countries, in both rural and urban settings [10]. The use of proven medications (aspirin, statins, and recommended blood pressure drugs) in patients with coronary heart disease or stroke is low, particularly in low-income countries, where 80% took no drugs (Figure 1). PURE also reported low rates of lifestyle changes in patients with CVD, as well as low rates of adherence to diet, physical activity and smoking cessation, particularly in low- and middle-income countries [11].

The economic status of the country accounted for about two-thirds of the variance in drug use; individual-level factors only accounted for one-third. The importance of this care gap was illustrated by a recent PURE publication, which showed that although the risk factor burden is lowest in low-income countries, the incidence rates of major CVD events and subsequent case fatality rates are substantially higher than in high-income countries [12]. This difference might be related to lower rates of preventive care, poorer management of people with pre-existing CVD and poorer care of people with acute cardiovascular events. Specifically for secondary prevention, it has been shown that the case fatality rates among patients with myocardial infarction, stroke or heart failure are higher in low- and middle-income countries than in high-income countries [12].
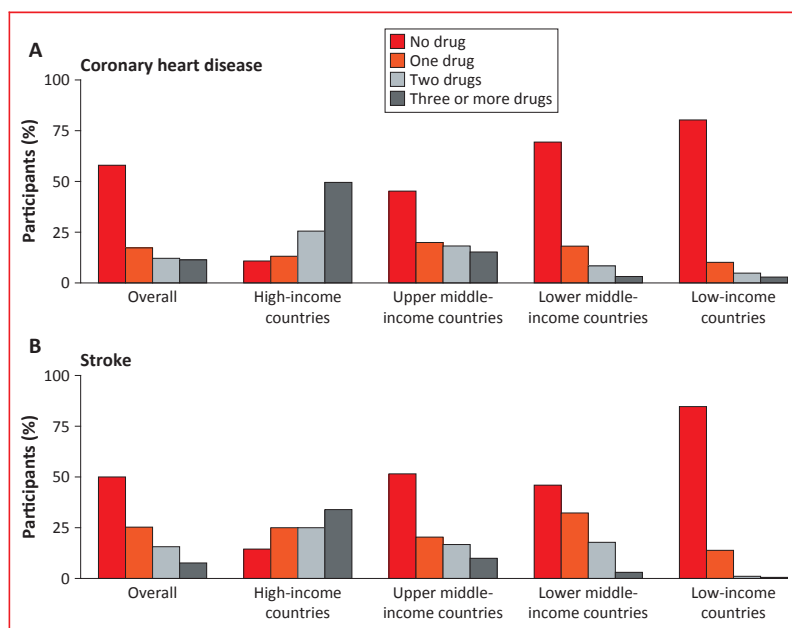
TABLE 1. Proportion of people with known CVD adherent to at least three priority interventions* and smoking cessation

	US	Europe	Upper middle-income countries	Lower middle Income countries	Low-income countries
At least three priority interventions	**48% (previous MI)** **41% (previous stroke)**	**79% (Previous MI)**	**21%**	**5%**	**4%**
Quit smoking	46%	51%	56%	43%	38%

MI, myocardial infarction. From Refs [11,15–17].
*Aspirin, statin and at least one blood-pressure-lowering drug.

Even in high-income countries, where secondary prevention interventions have increased in recent years, there are significant gaps. For example, in the US and Europe, suboptimal prescription and lifestyle modification rates are reported in patients with established coronary heart disease and stroke (Table 1) [13,14]. These findings suggest that health systems need to be modified to narrow the gaps in secondary prevention.

1.4. The treatment cascade

Healthcare professionals (HCPs) work within local, regional, and national health systems that can substantially influence which interventions are prioritized and how they are delivered. These environments can have a major effect on outcomes across populations. As shown in the Figure 2, there is a 'treatment effectiveness cascade' from the cardiovascular event to the long-term adherence with priority interventions. Therefore, even if an intervention has proven efficacy in clinical trials, its real-life effectiveness will be influenced by health system factors along the delivery chain, such as factors that affect prescription rates (health care provider level) and factors that affect adherence rates (patient level).

To reduce the gap between estimated efficacy and real-work effectiveness, it is vital to understand the potentially modifiable health system barriers at each level of the treatment effectiveness cascade and to develop and implement contextual strategies (facilitators) to overcome them [18].

1.5. Aim

The WHF Roadmap for secondary prevention aligns with the WHF goal of reducing premature mortality from CVD by at least 25% by 2025, and focuses on one target of the World Health Organization Global Action Plan for the Prevention and Control of Non Communicable Diseases (preventing heart attack and stroke through drug therapy and counselling for at least 50% of eligible populations). The aim of the WHF Secondary Prevention Roadmap is to summarize potential roadblocks along the continuum of clinical care for patients with known CVD and to identify potential solutions to overcome these roadblocks. The Roadmap includes case studies from low-, middle-, and high-income countries.

2. MAPPING THE HEALTH SYSTEM REQUIREMENTS TO ACHIEVE SECONDARY PREVENTION TARGETS

Two main actions are necessary to achieve the desired target for secondary prevention:

1. Priority interventions (ACE inhibitors, aspirin, statins, beta-blockers and strategies to facilitate lifestyle modification, particularly smoking cessation) should be recommended; and
2. Patients should be adherent to these recommendations.

To achieve these actions many health system conditions must be fulfilled (Table 2).

3. THE ROADMAP TO CARDIOVASCULAR SECONDARY PREVENTION TARGET

The health system requirements and conditions listed in the Table 2 are vital along the "journey" of patients with known CVD. Different roadblocks can appear at different stages of this journey and decrease the likelihood of achieving the stated secondary prevention target. Table 3 identifies roadblocks and potential solutions.
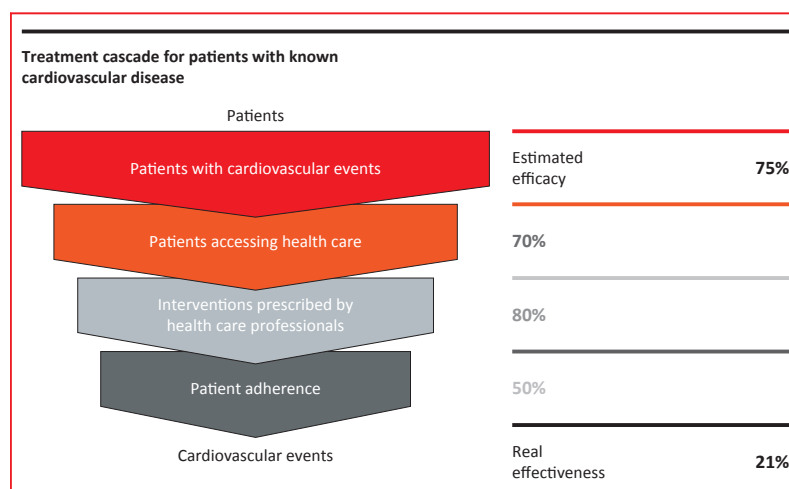

FIGURE 2. Four proven secondary prevention medications*: from efficacy to effectiveness Estimated efficacy of multi-drug therapy in preventing recurrent cardiovascular events [1]; other proportions are theoretical scenarios for illustration. *Statin, aspirin and ≥1 blood pressure-lowering agent.

TABLE 2. Health system requirements to achieve cardiovascular secondary prevention target

	Health system domains	Required conditions
	Human resources	**Availability of HCPs to prescribe proven therapies at hospital discharge and ensure their long-term use**
	Physical resources	Health care system facility available and accessible to patients when and where needed Availability of priority interventions at hospital and primary care or outpatient clinics within or near the community neighborhood
	Intellectual resources	**Availability of practical and locally relevant clinical guidelines**
	Healthcare delivery	Healthcare organized to integrate existing resources to ensure efficiency in the interaction between HCPs and patients and ensure that facilities are close to patients
	Healthcare recipient	**Patients aware and willing to follow recommendations**
	Financing	Patients can afford the access to healthcare facilities and recommended interventions Priority interventions are affordable to both the healthcare system and the patient Adequate level of investment in health care
	Governance	**Adequate political and regulatory framework supporting the strategy to implement and sustain priority interventions (including their availability and affordability)**
	Information System	A simple, timely, acceptable, and representative information system to provide reliable data about the incidence of fatal and non-fatal CVD events, prognosis and quality of care (including the use of priority interventions) of patients with known CVD

TABLE 3. Roadblocks, strategies and solutions to achieve cardiovascular secondary prevention target

Roadblock	Strategies	Potential solutions			
Patients with known CVD do not have access to the healthcare system	Improve access to the healthcare system	Strengthen the role of the primary care health system level for cardiovascular secondary prevention	Increase opening times of clinics, and locate them close to communities	Integrate secondary prevention interventions with simple cardiac rehabilitation programs	Integrate cardiovascular secondary prevention with management of other chronic conditions (HIV, tuberculosis)
Lack of HCPs to prescribe priority interventions	**Increase the availability of HCPs**	**Shift roles of HCPs towards allowing non-specialized workers to prescribe priority interventions**			
Guidelines are not available or recommendations are too complex	Simplify treatment	Develop simple and locally applicable guidelines	Simplify use of multiple drugs by using fixed-dose combinations	Pre-packaged blisters with multiple medications	
HCPs are not aware of guidelines	**Educate HCPs**	**Education**	**Audit and feedback**	**Decision support systems**	
HCPs are aware but do not follow guidelines	Ensure HCPs follow recommendations	Local opinion leaders	Financial incentives to promote care	Decision support systems	
Priority interventions are not available	**Increase availability of priority interventions**	**Include priority interventions in the national list of essential medicines**	**Improve efficiency of pharmaceutical distribution chain**	**Ensure that priority interventions are available at the secondary and primary care level**	**Ensure that priority interventions are available at the community level**
Priority interventions are not affordable	Universal health coverage	Promote the use of good quality, safe and inexpensive generic medications	Promote local manufacturing, bulk purchasing and/or efficient system to streamline medication supply	Provide financial and social support for patients to purchase priority interventions, or provide them free of charge (or at very low cost)	
Patients are not aware of the importance and need of long-term treatment	**Help patients adhere to recommendations**	**Education (health literacy)**	**Public campaigns**	**Empower patients to share decisions with HCPs**	
Patients do not remember to follow recommendations	Help patients adhere to recommendations	Use information and communication technology to remind patients about recommendations	Use fixed-dose combinations of key priority interventions to simplify treatment	Use patient-nominated, non-professional treatment supporters (spouse, friends, family)	

Proposed solutions for each strategy are provided in the following sections.

3.1. Increasing the access of patients with known CVD to the healthcare system

3.1.1. Integration of cardiovascular secondary prevention in primary care

Although the prescription of, and adherence to, priority interventions is frequently high at hospital discharge, adherence usually declines dramatically after six months [19]. Therefore, health systems with a strong primary healthcare approach (ensuring appropriate chronic care of patients with known CVD) are essential to scaling up the priority interventions.

Case study from Brazil [20]

> A recent study from Brazil evaluated the impact of its Family Health Program (FHP; the largest primary health care program in the world) on CVD. The study found that the annual FHP coverage reduced cerebrovascular disease mortality and heart disease mortality by 18% and 21% respectively. Moreover, FHP coverage increased the number of health education activities, domiciliary visits and medical consultations, and reduced hospitalization rates for cerebrovascular and heart disease.

3.1.2. Integration of cardiovascular secondary prevention interventions

Cardiac rehabilitation or preventive cardiology programs offering comprehensive management (including risk factor management, exercise and healthy diet recommendations) to patients with known CVD have been shown to be effective in some settings [21]. However, most of the studies were conducted in high-income countries and are resource intensive. Hence, many of these models would be difficult to implement in limited resource settings. Currently, only 23% of low- and middle-income countries offer cardiac rehabilitation programs; alternative sustainable models, tailored for these latter settings, should be designed, implemented and evaluated [22].

Case study from China. [23]

> A randomized controlled study of 167 coronary heart disease patients, conducted in China, showed that a 12-week hospital-initiated, home-based, multifaceted, nurse-led cardiac rehabilitation program improved walking, diet, and medication adherence. There was greater reduction in serum lipids and better control of systolic and diastolic blood pressure at 3 months.

3.2. Increasing the availability of HCPs to provide recommendations to patients with known CVD

In countries with an inadequate number of physicians, it has been shown that key elements of chronic disease management can be performed effectively by trained non-physician health workers (NPHW) with improved outcomes. Most of the evidence on NPHWs has been derived from studies evaluating maternal and child healthcare [24–26], although recent work shown its potential for non-communicable disease (NCD) [27]. For example, the Rural Andhra Pradesh Cardiovascular Prevention Study (RAPCAPS) showed that NPHWs could reliably identify individuals at high cardiovascular risk and that their recommendations for drug therapy in patients with known CVD were similar to those made by physicians [28]. The case study below describes additional work conducted in India showing the potential effect of this strategy.

Case study from India. [29]

> The *Secondary Prevention of Coronary Events After Discharge (SPREAD) study* was a randomized controlled trial evaluating a non-physician health worker (NPHW)-based intervention to improve adherence to medications and lifestyle modifications one year after acute coronary syndrome. A total of 806 patients in 13 Indian cities with a recent acute coronary syndrome were randomized at the time of discharge to either standard care or to intervention by NPHWs. At 1 year, a significantly greater proportion of patients in the intervention arm were adherent to the four classes of secondary prevention medications (97% vs. 92%; odds ratio: 2.62; 95% CI: 1.32, 5.19), had stopped smoking (79% vs. 49%; $p < 0.0001$), increased physical activity (89% vs. 60%; $p < 0.0001$), and were eating a healthy diet (median diet score 5 vs. 3; $p < 0.0001$). Systolic blood pressure was lower by 3.6 mmHg (control arm: 128 mmHg; intervention arm: 124.4 mmHg; $p = 0.0009$) and body mass index was lower by 0.6 kg/m^2 (control arm: 25.0 kg/m^2; intervention arm: 24.4 kg/m^2; $p = 0.038$). Overall, regular contact over 1 year between a NPHW and the patient and his/her family helped to improve adherence to evidence-based medications, healthy behaviors, and cardiovascular risk factors.

3.3. Simplifying the treatment of patients with known CVD

Greater complexity of treatments (number of drugs, doses, and frequency) decreases medication adherence. Fixed-dose combination therapy is a potential solution to simplify prescription, to decrease drug stock-outs (because of a streamlined supply chain), increase patient adherence, and to reduce costs. Fixed-dose combinations are commonly used for HIV, tuberculosis, and hypertension [30], and combinations are also common in most cancers.

Their use in the secondary prevention of CVD was proposed in 2002 by Yusuf [1] and was extended to primary prevention by Wald [31]. The degree of lowering of blood pressure and low-density lipoprotein (LDL)-cholesterol

with fixed-dose combinations could reduce the risk of CVD by 60–70% relative to placebo [32].

Although their role in primary prevention is still debated, several studies in high-risk patients (including those with existing CVD) have shown that they increase adherence without an increase in adverse effects [33,34]. There is a general consensus on the potential effectiveness of fixed-dose combinations in secondary prevention [35].

Case studies on fixed-dose combination therapy trials. [33,34]

> *FOCUS trial:*
> This study evaluated the effect of a polypill (containing aspirin 100 mg, simvastatin 40 mg, and ramipril 2.5, 5 or 10mg) compared with the three drugs given separately, for nine months, in 695 patients with previous myocardial infarction. The polypill group showed improved adherence compared with the group receiving separate medications (51% vs. 41%, respectively; p = 0.019). There were non-significant differences in systolic blood pressure and LDL-cholesterol.
>
> *SPACE collaboration:*
> This collaboration involved three studies conducted from 2009 to 2013: UMPIRE with 1,000 patients from India and 1,004 from western Europe; Kanyini-GAP with 623 patients from Australia; and IMPACT with 513 patients from New Zealand. In the Australasian trials, half of the patients were indigenous. Each trial compared the effects of a fixed-dose combination (containing aspirin, lisinopril, simvastatin, and either atenolol or hydrochlorothiazide) with usual care. A prospective meta-analysis indicated a 43% proportional increase in adherence to aspirin, statin, and ≥2 blood pressure lowering drugs in the combination group at 12 months, together with significant improvements in blood pressure and LDL-cholesterol. The improvements in adherence were largest among patients not taking all of the recommended treatments at baseline.

Case studies from the United States and Europe

> *Get With The Guidelines® (GWTG)*
> Get With The Guidelines® (GWTG) is a comprehensive set of programs from the American Heart Association/American Stroke Association (AHA/ASA) whose objective is to translate clinical guidelines into clinical practice. The programs include heart failure, stroke, resuscitation, atrial fibrillation and systems of care related to ST elevated myocardial infarction (STEMI) and non-STEMI. The AHA/ASA's Quality and Systems Improvement staff work with participating hospitals and health systems to implement the programs using quality improvement consultation, workshops, and webinars. In addition, the AHA uses clinical databases to allow hospitals to collect information for the assessment of quality and regional/national benchmarking. The GWTG has published over 300 articles in peer-reviewed journals, reporting a wide range of achievements. These include substantial improvements in adherence with evidence-based therapies, development of successful implementation strategies, development of clinical and outcomes measures, and overall improvements in the quality of care.
>
> *The European Association for Cardiovascular Prevention and Rehabilitation (EACPR) Prevention Implementation Program*
> The main objective of this program is to provide practical implementation tools to improve clinical practice and influence national policy on CVD prevention. HCP toolkits have been developed with useful resources to facilitate implementation of European Guidelines on CVD Prevention into daily practice. National CVD Prevention Coordinators have been appointed in European Society of Cardiology member countries to facilitate the endorsement, adaptation, translation and publication of these guidelines. More information is available at:
>
> - www.heart.org/HEARTORG/HealthcareResearch/GetWithTheGuidelinesHFStroke/Get-With-The-Guidelines—HFStroke_UCM_001099_SubHomePage.jsp
> - www.escardio.org/COMMUNITIES/EACPR/Pages/welcome.aspx

3.4. Ensuring that HCPs follow recommendations

Many strategies have been evaluated to increase the use of clinical guidelines among HCPs, including audit and feedback, clinical decision support systems, use of local opinion leaders, and education [36]. Most of these studies were not disease-specific, but it is reasonable to assume that the evidence can likely be extrapolated from other chronic conditions to cardiovascular secondary prevention.

Although many of the strategies were effective, their effects were generally modest, and multifaceted interventions are recommended for changing the behavior of healthcare providers. Large organizations focused on CVD have been implementing educational initiatives to improve cardiovascular secondary prevention.

3.5. Increasing the availability and affordability of key priority interventions

The PURE study collected medication cost data from 598 communities in 18 high-, upper middle-, lower middle-, and low-income countries (HIC, UMIC, LMIC, LIC). Availability was lower in LIC (particularly in rural areas) in comparison with HIC [37]. Affordability was defined as the ratio of expenditure on medications (cost to the patient) to total household resources. Previous work had suggested that a household cannot afford to purchase medications if they cost ≥20% of the household's resources [38]. Using this definition, data indicate that 0.14% of households in HIC, 25% in UMIC, 33% in LMIC, and ~60% in LIC could not afford the four cardiovascular secondary prevention medications.

In a statistical model adjusted for factors that influence medication use, patients with a history of CVD from low- and middle-income countries were 60% less likely to use these medications if they were unaffordable (odds ratio: 0.40; 95% CI: 0.24−0.65). Although medication costs are up to 50% lower in LIC compared with HIC, there remains a 10−20-fold difference in household incomes, which largely explains why medications remain less affordable in LIC.

With this combined lower availability and affordability, it is not surprising that there is low coverage of secondary prevention medications in LMIC and LIC.

The following strategies have been proposed to increase the affordability of cardiovascular medicines [40,41]:

1. Increase the efficiency of the medication supply chain to promote access to medicines within existing health budgets (through more efficient selection, quantification and forecasting, procurement, storage, and distribution of medications);
2. Promote the use of generic medications (particularly combinations) by overcoming legal barriers relating to patents and licenses;
3. Develop policies to reduce end-user prices, including regulating retail mark-ups and eliminating tariffs on medicines; and
4. Engage the private sector to price CVD medicines at affordable levels in LMICs.
5. Provision of free essential drugs through universal health coverage

Engagement with innovative companies to advance access strategies should also be encouraged.

Given the increasing global interest in universal health coverage, a potentially powerful solution would be to ensure that governments provide priority cardiovascular secondary prevention interventions free of charge (or at very low cost).

Case study from HIV and the President's Emergency Plan for AIDS Relief (PEPFAR). [39]

> The effectiveness of policies for improving the use of medications in the secondary prevention of CVD is not well documented. However, lessons can be learned from policies aimed at other conditions, such as improvements in access to anti-retroviral medicines (ARVs). The effects of the US President's Emergency Plan for AIDS Relief (PEP-FAR) on cost savings from switching to procurement of generic ARVs in 16 low- and middle-income countries were examined. Estimated yearly savings increased from $8.1 million in 2005 to $214.6 million in 2008, allowing these countries to shift funds from their ARV budget and invest in other priority programs. This also allowed PEPFAR to increase the use of ARVs and to provide treatment for nearly four million people. There is an urgent need to evaluate the effectiveness of strategies to increase the availability and affordability of simple, effective cardiovascular secondary prevention medications.

3.6. Helping patients to adhere to recommendations

Once priority cardiovascular secondary prevention interventions are recommended by HCPs and are available and affordable, then patients need to follow these recommendations. This step is particularly challenging with secondary cardiovascular prevention because most of the interventions are lifelong treatments, and many patients may be asymptomatic.

To improve adherence, provision of information alone is not effective; behavior change approaches are needed. A 2014 systematic review provided insights into the patient factors that influence adherence to secondary prevention medications [42]. Fatalistic beliefs about their disease or beliefs that they had already been cured decreased adherence. Relationships with prescribing HCPs were also reported as very important for patients, with complex terminology negatively affecting perceptions about treatments.

The widespread ownership of mobile phones (even in LIC) provides potential to deliver behavior change interventions to large numbers of people at low cost. Text messages have been shown to improve medication adherence for a variety of conditions (such as HIV). Their use for secondary prevention is promising, although, to the best of our knowledge, there is not yet any specific evidence in this context [43,44]. However, there have been studies that used postal reminders, which showed some (modest) effect on adherence.

Case study from the United States. [45]

> A randomized controlled trial of 836 post-myocardial infarction patients in the United States evaluated the effect of a simple direct-to-patient reminder on beta-blocker adherence. The intervention consisted of two mailed communications: a personalized letter, followed by a similar letter ∼2 months later and an accompanying brochure. The communications stressed the importance of lifelong use of beta-blockers and the need for refills, and discussed the management of potential adverse effects. Patients in the treatment arm were 17% more likely to be adherent to beta-blockers at 9 months after the first mailing (relative risk: 1.17; 95% CI: 1.02−1.29).

3.7. Strengthening the governance of healthcare systems to enhance prevention

The successful implementation of all of the solutions mentioned above is highly dependent on governance structures and stewardship (from ministerial to the primary healthcare level). Strengthening national leadership can increase the likelihood of scale-up success. Therefore, a parallel investment in leadership development is essential to the successful scale-up of secondary prevention interventions.

Case study from Australia

Australia National Secondary Prevention Alliance
    The Australia National Secondary Prevention Alliance was established in May 2013 and comprises representatives from 19 national healthcare, consumer, government, and non-governmental organizations, representing public and private healthcare, primary care, medical health professionals, nursing, allied health, consumer and Indigenous groups. The Alliance has agreed on three strategic directions. They include: (1) increasing awareness of the need for lifelong preventive care in people with heart disease; (2) strengthening primary care; and (3) improving data and quality across Australia. The overarching vision is to improve lifelong outcomes. Key successes so far have included the establishment and commitment across organizations, awareness campaigns (including production of a video and extensive media coverage), government lobbying, and pilot implementation work designed to inform policy change. In addition, four working groups have been established to address the following priority areas: strengthening primary care; developing the workforce and accreditation; national resource to support patient self-management; and quality improvement.

3.8. Strengthening health information systems

Most countries do not have reliable information about the incidence of CVD, prognosis, and quality of care of patients with known CVD. Hence, the allocation of resources to tackle specific problems is not evidence-based and it is likely that the limited resources available will not be allocated appropriately or efficiently. This limitation can be overcome by the establishment of simple, representative and timely information systems for patients with known CVD (and for those with hypertension and other common conditions). Such systems should be established in the context of a broader NCD surveillance strategy, and should be tailored according to the specific setting.

3.8.1. High middle- and high-income countries

In well-resourced countries with mature healthcare systems, national or regional registries (complemented by electronic health records and further information from the general population) can provide complete and updated information.

3.8.2. Lower middle- and low-income countries

In countries with poor resources and less developed healthcare systems, a pragmatic approach would be to collect essential health information through brief, periodic surveys (e.g., every 3—5 years) from large, representative samples of households. The Kerala Health Observatory has shown the reliability of such an approach, using only one key informant to collect simple data on all members of a household. This improves

Case study from the United Kingdom and the United States. [46,47]

Myocardial Ischaemia National Audit Project (MINAP)
    The Myocardial Ischaemia National Audit Project (MINAP) is a national registry of patients admitted to all hospitals in England and Wales with acute coronary syndromes. It provides participating hospitals with a record of their management compared with national standards of care. Analyses of performance in key areas are updated every 24 hours and made available to hospitals and ambulance services. Participating hospitals can only view analyses relating to their own patients, compared against national aggregate data. In addition, hospitals can generate quarterly audit reports and can download their own data for local analyses. At a national level, MINAP delivers an annual audit report of process measures, as well as 30-day mortality for individual hospitals. More information is available at: www.ucl.ac.uk/nicor/audits/minap.
    The National Cardiovascular Data Registry PINNACLE (Practice Innovation and Clinical Excellence) registry
    This is the largest outpatient quality improvement registry of patients treated in ambulatory cardiology clinics in the US. It was launched by the American College of Cardiology Foundation in 2008. Participating practices collect patient data at the point of care for each outpatient visit. This includes demographics, comorbidities, symptoms, vital signs, medications, contraindications and laboratory values. Data are collected by exporting a practice's electronic health record and the process is standardized through written definitions, uniform data entry and transmission requirements, and data quality checks. In 2012, the American College of Cardiology (ACC), in collaboration with local stakeholders, launched the PINNACLE India Quality Improvement Program [48]. This program collects data on the quality of outpatient care for cardiovascular risk factors (hypertension, diabetes mellitus) and disease states (coronary artery disease, heart failure, atrial fibrillation). The database receives clinical data from paper scanners and an electronic data collection tool. Patients are also followed longitudinally if they return to a data-collecting outpatient site. Participants receive quarterly reports that compare outpatient departments and individual clinicians against national benchmarks on ACC performance metrics. More information is available at: www.ncdr.com/WebNCDR/home/aboutthencdr.

the efficiency and speed of such surveys and helps to reduce cost.
    These surveys could collect data on key health indicators at a population level, to inform cardiovascular prevention health policies, such as: (1) mortality and morbidity (e.g., hospitalization) by cause over the *previous* three years; (2) behaviors and risk factors that influence the prognosis of patients with CVD, healthcare utilization, and healthcare expenditure; and (3) information on the utilization of healthcare resources, including their availability, distance, access and affordability.

Case study from India

A model to document risk factors and treatments in a representative sample in resource-challenged settings

This approach is currently being developed in a state in India to better characterize the health profile of the population and to guide policy decisions. In this model, a mixed sampling method is used to identify a representative sample of households in the state and to allow comparisons between major districts. Essential health data pertaining to deaths, hospitalizations, NCDs, risk factors, health-related behaviors, healthcare utilization and health expenditure are collected from a survey given to all individuals in a selected household. The survey is administered through an existing network of government community health workers that have access to all communities within the state. Information is collected electronically and transferred directly from the field to a central site for additional processing and analysis. Results are then provided to health policy makers to inform strategies aimed at strengthening the health system.

Stratified sampling of all districts in the state

Cluster sampling of communities in each district

Random sampling of the first household in each selected community. Convenience sampling of 54 additional households

Community health workers administer survey using electronic handheld devices

Selection of all individuals in households

Real time data quality checks and data transfer centrally

Data collection: deaths, hospitalizations, NCD's, risk factors, health related behaviors, health care access and health expenditures

The sampling strategy should attempt to create a broadly representative sample of the target population. Mixed sampling is typically needed, with random sampling of households improving the representativeness of the survey; stratified sampling providing adequate representation between regions of interest (e.g., states); and if cluster sampling is used, a probability proportional to size strategy can be employed to ensure that larger clusters have greater representation.

In some countries, infrastructure may already be in place with access to communities (e.g., NGOs, government community health workers, or programs for vaccination or malaria control). Using this can significantly reduce the costs associated with survey implementation. Electronic data collection (while simultaneously getting GPS coordinates) may increase upfront costs, but real-time data quality checks and the ability to directly transfer data from the field in real time can decrease the organizational costs

associated with data processing, while maintaining data quality. Furthermore, GPS coordinates can be used to overlay information on the environment, access to health facilities and proximity to roads and emission sites (e.g., factories) and can also be linked with data on air quality and other secondary information.

Periodic surveys can be performed every 3–5 years to document changes at the population level in the common causes of mortality and morbidity, NCD prevalence and risk factors.

3.9. The cardiovascular secondary prevention roadmap

Based on the information provided in previous sections, an "ideal" journey for patients with known CVD should include the following components:

1. Healthcare systems should be accessible not only during the acute phase, but also during longitudinal follow-up to ensure lifelong care.
2. Practical clinical guidelines recommending priority interventions should be available.
3. HCPs who can prescribe according to recommendations should be available.
4. Priority cardiovascular secondary interventions should be available and affordable to patients.
5. Patients should be given help to better adhere to recommendations.
6. An information system should be in place to monitor progress in CVD prevention.

Barriers should be explored according to the specific settings and solutions be tailored accordingly. However, some of the most important solutions suggested in the Roadmap, which are particular relevant for low- and middle-income countries, are presented in Box 4.

BOX 4 Roadmap for secondary prevention

1. **Strengthen the role of primary care providers in cardiovascular secondary prevention.**
2. **Share the roles of HCPs with trained non-physician health workers, by allowing non-specialized workers to prescribe priority interventions.**
3. **Develop simple and practical guidelines.**
4. **Use low cost fixed-dose combinations (if available) of key priority interventions to simplify treatment and increase adherence.**
5. **Ensure that priority interventions are available at secondary, primary and community levels.**
6. **Promote the use of good quality, low cost and affordable generic medications.**
7. **Provide financial and social support for patients to purchase priority interventions.**
8. **Use information and communication technology to support clinical decision making and increase patient adherence.**
9. **Develop simple, representative and timely information systems for patients with known CVD.**
10. **Establish accountable governance structures from ministerial to the primary healthcare level (including national CVD plans).**

4. CONCLUSIONS

The value of cost-effective cardiovascular secondary prevention interventions has been known for over a decade. However, their uptake is still unacceptably low, particularly in low- and middle-income countries where the case fatality rate for CVD is higher than in high-income countries [12]. The widespread use of proven secondary prevention interventions is vital to reduce the risk of CVD in those with vascular disease and will be a critical step to reducing CVD premature mortality by 25% by 2025.

The WHF Secondary Prevention Roadmap describes the barriers at different health systems levels to the implementation of priority cardiovascular secondary prevention measures. It also proposes potential solutions that have been shown to be effective in overcoming them.

This Roadmap is only the starting point and provides general guidance. The final paper in this *Global Heart* issue provides further guidance on how it should be adapted locally, according to barriers and solutions that are relevant in specific regional and national settings.

REFERENCES

1. Yusuf S. Two decades of progress in preventing vascular disease. Lancet 2002;360:2–3.
2. World Health Organization. World Health Report 2002: Reducing risks, promoting healthy life. Available at: www.who.int/whr/2002/en/whr02_en.pdf. Accessed March 27, 2015.
3. Chambless L, Keil U, Dobson A, et al. Population versus clinical view of case fatality from acute coronary heart disease: results from the WHO MONICA Project 1985—1990. Multinational MONitoring of Trends and Determinants in Cardiovascular Disease. Circulation 1997; 96:3849–59.
4. Kerr AJ, Broad J, Wells S, Riddell T, Jackson R. Should the first priority in cardiovascular risk management be those with prior cardiovascular disease? Heart 2009;95:125–9.
5. Lim SS, Gaziano TA, Gakidou E, et al. Prevention of cardiovascular disease in highrisk individuals in low-income and middle-income countries: health effects and costs. Lancet 2007;370:1954–62.
6. Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 2011;124:2458–73.
7. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (Version 2012). Eur Heart J 2012;33:1635–701.
8. World Health Organization. Prevention of recurrent heart attacks and strokes in low and middle income populations. Evidence-based recommendations for policy makers and health professionals. Available at: www.who.int/cardiovascular_diseases/resources/pub0402/en/. Accessed March 27, 2015.
9. Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. Cochrane Database Syst Rev 2003; 4:CD003041.
10. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 2011;378:1231–43.
11. Teo K, Lear S, Islam S, et al. Prevalence of a Healthy Lifestyle Among Individuals with Cardiovascular Disease in High-, Middle- and Low-Income Countries. The Prospective Urban Rural Epidemiology (PURE) Study. JAMA 2013;309:1613–21.
12. Yusuf S, Rangarajan S, Teo K, et al. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. N Engl J Med 2014;371: 818–27.
13. Kotseva K, Wood D, De Backer G, et al. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet 2009;373:929–40.
14. Maddox TM, Chan PS, Spertus JA, et al. Variation in secondary prevention prescription among outpatient cardiology practices: insights from the NCDR. J Am Coll Cardiol 2014;63:539–46.
15. Kotseva K, personal communication (EUROASPIRE IV).
16. Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) 2009—2010. Available at: wwwn.cdc.gov/nchs/nhanes/search/nhanes09_10.aspx. Accessed March 27, 2015.
17. Dawood N, Vaccarino V, Reid KJ, et al. Predictors of Smoking Cessation After a Myocardial Infarction The Role of Institutional Smoking Cessation Programs in Improving Success. Arch Intern Med 2008;168:1961–7.
18. Nieuwlaat R, Schwalm JD, Khatib R, Yusuf S. Why are we failing to implement effective therapies in cardiovascular disease? Eur Heart J 2013;34:1262–9.
19. Eagle KA, Kline-Rogers E, Goodman SG, et al. Adherence to evidence-based therapies after discharge for acute coronary syndromes: an ongoing prospective, observational study. Am J Med 2004;117:73–81.
20. Rasella D, Harhay MO, Pamponet ML, et al. Impact of primary health care on mortality from heart and cerebrovascular diseases in Brazil: a nationwide analysis of longitudinal data. BMJ 2014;348:1–10.
21. Clark A, Hartling L, Vandermeer B, McAlister F. Secondary prevention programs for patients with coronary artery disease: A meta-analysis of randomized control trials. Ann Intern Med 2005;143:659–72.
22. Turk-Adawi K, Sarrafzadegan N, Grace SL. Global availability of cardiac Rehabilitation. Nat Rev Cardiol 2014;10:586–96.
23. Jiang X, Sit JW, Wong TK. A nurse-led cardiac rehabilitation programme improves health behaviours and cardiac physiological risk parameters: evidence from Chengdu, China. J Clin Nurs 2007;16:1886–97.
24. Lewin S, Lavis JN, Oxman AD, et al. Supporting the delivery of cost-effective interventions in primary health-care systems in low-income and middle-income countries: an overview of systematic reviews. Lancet 2008;372:928–39.
25. van Ginneken N, Tharyan P, Lewin S, et al. Non-specialist health worker interventions for the care of mental, neurological and substance-abuse disorders in low- and middle-income countries. Cochrane Database Syst Rev 2013;11:CD009149.
26. World Health Organization. Task-Shifting: rational redistribution of tasks among health workforce teams: global recommendations and guidelines. Available at: www.who.int/healthsystems/TTR-TaskShifting.pdf. Accessed March 27, 2015.
27. Joshi R, Alim M, Kengne AP, et al. Task Shifting for Non- Communicable Disease Management in Low and Middle Income Countries — A Systematic Review. PLoS ONE 2014;9:e103754.
28. Joshi R, Chow C, Raju PK, et al. The Rural Andhra Pradesh Cardiovascular Prevention Study. JACC 2014;59:1188–96.
29. Kamath DY, Xavier D, Gupta R, et al. Rationale and design of a randomized controlled trial evaluating community health worker—based interventions for the secondary prevention of acute coronary syndromes in India (SPREAD). Am Heart J 2014;168:690–7.
30. Connor J, Rafter N, Rodgers A. Do fixed-dose combination pills or unit-of-use packaging improve adherence? A systematic review. Bull World Health Organ 2004;82:935–9.

31. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003;326:1419–25.

32. Yusuf S, Pais P, Afzal R, Xavier D, Teo K, Eikelboom J, et al. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. Lancet 2009;373(9672):1341–51.

33. Castellano JM, Sanz G, Peñalvo JL, et al. A polypill strategy to improve adherence: results from FOCUS (Fixed-dose Combination Drug for Secondary Cardiovascular Prevention) Project. J Am Coll Cardiol 2014;64:2071–82.

34. Webster R, on behalf of the SPACE Collaboration. The Single Pill to Avert Cardiovascular Events (SPACE) Collaboration: Main results. Presented at the World Congress of Cardiology. Melbourne, Australia. May 4–7, 2014.

35. Huffman M, Yusuf S. Polypills Essential Medicines for Cardiovascular Disease Secondary Prevention? J Am Coll Cardiol 2014;63: 1368–70.

36. Grimshaw JM, Eccles MP, Lavis JN, Jill SJ, Squires JE. Knowledge translation of research findings. Implement Sci 2012;7:50.

37. Rasha Khatib personal communication (PURE Study)

38. Niëns LM, Van de Poel E, Cameron A, Ewen M, Laing R, Brouwer WBF. Practical measurement of affordability: an application to medicines. Bull WHO 2012;90:219–27.

39. Holmes CB, Coggin W, Jamieson D, et al. Use of Generic Antiretroviral Agents and Cost Savings in PEPFAR Treatment Programs. JAMA 2010; 304:313–20.

40. Kishore SP, Vedanthan R, Fuster V. Promoting Global Cardiovascular Health Ensuring Access to Essential Cardiovascular Medicines in Low- and Middle-Income Countries. J Am Coll Cardiol 2011;57: 1980–7.

41. Hogerzeil HV, Liberman J, Wirtz VJ, et al. Promotion of access to essential medicines for non-communicable diseases: practical implications of the UN political declaration. Lancet 2013;381: 680–9.

42. Rashid MA, Edwards D, Walter FM, Mant J. Medication taking in coronary artery disease: a systematic review and qualitative synthesis. Ann Fam Med 2014:224–32.

43. Free C, Phillips G, Galli L, et al. The effectiveness of mobile-health technology-based health behaviour change or disease management interventions for health care consumers: a systematic review. PLoS Med 2013;10:e1001362.

44. Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. Cochrane Database Syst Rev 2012;3: CD009756.

45. Smith DH, Kramer JM, Perrin N, et al. A randomized trial of direct-to-patient communication to enhance adherence to betablocker therapy following myocardial infarction. Arch Intern Med 2008;168: 477–83.

46. Herrett E, Smeeth L, Walker L, Weston C, MINAP Academic Group. The Myocardial Ischaemia National Audit Project (MINAP). Heart 2010;96:1264–7.

47. Maddox TM, Chan PS, Spertus JA, et al. Variations in coronary artery disease secondary prevention prescriptions among outpatient cardiology practices: insights from the NCDR (National Cardiovascular Data Registry). J Am Coll Cardiol 2014;63:539–46.

48. Risch SA, Vicera VD, Glusenkamp NT, et al. Documented medication use among coronary artery disease outpatients in India: Insights from PINNACLE India outpatient registry. Circ Cardiovasc Qual Outcomes 2014;7:A179.